REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Applicants have amended the specification and submitted replacement sheets for Figures 1–6 of the drawings. No new matter has been added by way of these amendments.

Claims 1–27 have been canceled, claims 28, 30, 31, 33 and 34 have been amended, and new claims 49 and 50 have been added. Support for the amendment to claim 28 is found in the specification at pg. 23, lines 2–9 and pg. 29 line 25 thru pg. 30, line 2. Support for new claim 49 is found on pg. 14, lines 10–22; pg. 41, lines 20–25; and Figure 3. Support for new claim 50 is found on pg. 23, lines 2–8. Accordingly, no new matter has been added by way of these amendments.

The rejection of claims 28–31, 33, and 34 under 35 U.S.C. § 112 (second paragraph) for lack of clarity is respectfully traversed in view of the above amendments.

The rejection of claims 28–31, 33, and 34 under 35 U.S.C. § 112 (first paragraph) for lack of enablement is respectfully traversed.

The United States Patent and Trademark Office ("PTO") has taken the position that the specification provides only literal support and does not provide direction or guidance for a skilled scientist to perform the claimed method of treating a patient having a neurodegenerative disease characterized by extracellular plaques with a reasonable expectation of success. Moreover, the PTO asserts that because the specification teaches that increased exposure to HSV amplicon vectors causes death of the exposed subject, one of skill in the art would not reasonably expect that any therapeutic effect would be seen in the subject prior to death. Applicants respectfully disagree for several reasons.

Firstly, the examples of the present application demonstrate that the skilled artisan can practice the claimed invention. In particular, the examples describe the construction of HSV amplicons containing a transgene (*i.e.*, a nucleic acid encoding the amyloid-β_{1-42} ($A\beta_{1-42}$) peptide with and without the tetanus toxin Fragment C (TtxFC) molecular adjuvant) (*see* specification at pg. 34, lines 8–34). The examples further describe helper virus-free amplicon packaging and administration of HSV amplicon particles containing $A\beta_{1-42}$ (HSVAβ) alone, $A\beta_{1-42}$ and TtxFC (HSVAβ/TtxFC), or lacZ (control) to Tg2576 mice, a transgenic animal model of Alzheimer's disease (AD) (*id.* at pg. 34, lines 28–30 and pg. 35, lines 5–14). Further, the generation of an Aβ specific antibody response in both Tg2576 and wildtype mice following amplicon particle administration is reported on pg. 40, line 25

thru pg. 41, line 11 of the specification. Finally, the observed reduction in Aβ plaque burden in Tg2576 mice administered HSVAβ/TtxFC as assessed by Aβ immunohistochemistry and Thioflavin-S histochemistry is reported at pg. 43, lines 5–28 of the specification.

Secondly, although the PTO asserts that the specification teaches exposure to the HSV amplicon causes death in a subject, as explained within the examples of the present invention, the observed mortality was an amplicon-specific and genotype-specific event that occurred only in the Tg2576 mice receiving the HSVAβ amplicon (*see* specification at pg. 42, lines 1–12 and Figure 6). This mortality was not observed in non-transgenic amplicon treated animals or Tg2576 transgenic animals receiving control or HSVAβ/TxFC amplicons (*id.*). In fact, as shown in Figure 6, all but one non-transgenic animal receiving either the HSVlac, HSVAβ, or HSVAβ/TtxFc treatment survived administration. Likewise, all Tg2575 transgenic animals receiving the HSVAβ/TtxFc amplicon particle survived, and only one Tg2576 transgenic animal that received the HSVlac amplicon particle failed to survive. One of skill in the art would readily appreciate that because the observed mortality was amplicon-specific and genotype-specific, the claimed method can still be carried out with a reasonable expectation of success.

Applicants further submit that Frazer et al., "Reduced Pathology and Improved Behavioral Performance in Alzheimer's Disease Mice Vaccinated with HSV Amplicons Expressing Amyloid-β and Interleukin-4," *Mol. Ther.* 16(5):845–853 (2008) ("Frazer"), attached hereto as Exhibit 1, is evidence demonstrating that the present invention enables one of skill in the art to treat a patient having a neurodegenerative disease characterized by extracellular plaques. In particular, Frazer describes administering HSV amplicon particles expressing the $A\beta_{1-42}$ peptide and the IL-4 adjuvant to a triple transgenic AD (3xTg-AD) mouse model, which is a different animal model of AD than the Tg2576 model of the present invention (*see* Frazer at pg. 846, col. 1, para. 2 and Fig. 1). The HSV amplicon particles of Frazer were produced using a helper virus-free method that involved transfecting a cell with (a) an amplicon plasmid comprising an HSV origin of replication, an HSV cleavage/packaging signal, and a nucleic acid encoding the $A\beta_{1-42}$ peptide and IL-4, (b) one or more vectors that, individually or collectively, encode all essential HSV genes but exclude all cleavage/packaging signals, and (c) a nucleic acid encoding an accessory protein (*see* Frazer at page 851, col. 2., para. 3, *citing* Bowers et al., "Expression of vhs and VP16 during HSV-1 Helper Virus-Free Amplicon Packaging Enhances Titers," *Gene Ther.* 8:111–120 (2001) at page 117, col. 2, para. 2, for the helper virus-free packaging methodology, attached hereto as Exhibit 2). Following HSV amplicon administration to 3xTg-AD mice, Frazer reports that an increase in Aβ specific antibody

production, improved learning and function of memory, and prevention of AD-related amyloid and tau pathological progression were observed (*see* Frazer at 846, col. 1, para. 2). In addition, Frazer does not report any mortality associated with amplicon particle delivery in either wildtype or transgenic animals, supporting the amplicon- and genotype-specificity of the mortality described in the present application. Accordingly, as demonstrated by Frazer, the present application fully enables one of skill in the art to carry out the claimed invention.

The PTO further asserts that the specification fails to enable the administration or co-administration of a helper virus. However, as recited in claim 28, the HSV amplicon particle administered to a patient is made using a *helper virus-free method* that involves transfecting a cell with (a) an amplicon plasmid comprising an HSV origin of replication, an HSV cleavage/packaging signal, and the heterologous transgene, (b) one or more vectors that, individually or collectively, encode all essential HSV genes but exclude all cleavage/packaging signals, and (c) a nucleic acid encoding an accessory protein. As described above, the specification fully enables the administration of an HSV amplicon particle made using helper virus-free methodology.

For all of the forgoing reasons, applicants submit that the rejection of claims 28–31, 33, and 34 under 35 U.S.C. § 112 (first para.) for lack of enablement is improper and should be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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